REMARKS

Claims 1-80 were pending prior to this Response. By the present communication, claims 1, 5, 16, 22, 24, 28, 31, 48, 50, 57, 59, 60, 62, 64-66, 69, 71 and 79 have been amended to define Applicants' invention with greater particularity. No new matter is added, the new claim language being fully supported by the Specification and original claims. Accordingly claims 1-80 are currently pending.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 28-56 and 66 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse this rejection. With regard to claim 28 (and those dependent thereon), the Examiner alleges that the body of claim 28 does not recite any steps wherein the tissue is electroporated. However, by the present communication, claim 28 has been amended to require administration of at least one electric pulse having sufficient strength and duration to cause electroporation of the region of skin, thereby delivering L-ascorbic acid or a derivative thereof through the stratum corneum of the skin. Applicants submit that the amendment to claim 28 requiring "electroporation of the region of skin" obviates the rejection as to claims 28-56.

With regard to claim 66, the Examiner alleges there is lack of antecedent basis for the phrase "said electrode mounting bracket." By the present communication, the dependency of claim 66 has been changed from claim 61 to claim 63, thereby obviating the rejection as to claim 66.

In view of these amendments, Applicants respectfully submit that all pending claims are definite and request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Rejection under 35 U.S.C. § 102(b)

A. Applicants respectfully traverse the rejection of claims 1-4, 7, 8, 20, and 27 under 35 U.S.C. § 102(b) as allegedly being anticipated by U. S. Patent No. 4,474,570 to Ariura et al. (hereinafter "Ariura"). Applicants' invention method for treating degenerative skin conditions by electroporation-delivered L-ascorbic acid and derivatives thereof, as required by present claim 1, distinguishes over the disclosure of Ariura by requiring application of "at least one electric pulse having sufficient strength and duration *to cause electroporation of the skin*, thereby delivering an effective amount of the L-ascorbic acid through the stratum corneum of the region of skin so as to improve the skin condition without substantial pain or skin irritation."

Applicants respectfully submit that Ariura fails to disclose using at least one electric pulse that causes electroporation of the skin in conjunction with application thereto of a composition comprising L-ascorbic acid, or a cosmetically/pharmaceutically acceptable salt, ester or other derivative thereof. Rather, Ariura discloses application of a single electrical pulse of 10-50 $\mu A/cm^2$, a pulse suitable for causing iontophoresis, but not suitable for electroporation and penetration of an active agent through the stratum corneum. In fact, Ariura is completely silent regarding delivery of the active compound "through the stratum corneum." Therefore, Applicants submit that Ariura fails to disclose each and every element of claim 1 (and claims 2-4, 7, 8, 20 and 27 dependent thereon) as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b).

B. Applicants respectfully traverse the rejection of claims 57, 59-64, 67-68, 72-74 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,464,386 to Hofmann (hereinafter "Hofmann"). The invention handheld pulser, as defined by amended claim 57, distinguishes over the pulser described by Hofmann by reciting "a support member of a size and shape to be handheld, an electrode detachably attached to the support member and operatively connected to a pulse generator; wherein the pulse generator and the electrode are configured to establish an electric field sufficient to transiently permeabilize stratum corneum when a voltage pulse in the range from about 25 V to about 50 V is delivered to the electrode by the pulse generator (Emphasis added).

The Hofmann pulser comprises a portion of support member 10 referred to as a "handle", which is suitable for gripping by hand, but Hofmann is absolutely silent regarding a pulser that is sized and shaped to be handheld (i.e., unattached to a stationery body). In fact, as shown in Figure 1, the Hoffmann support member includes a table mounting device at its base. In addition, although the Examiner refers to an allegedly "detachable electrode 22" in the Hofmann device, Hofmann, in fact, does not disclose that the electrode is "detachable." Instead, Hofmann describes the electrode as flexibly attached to head assembly 16: "The head assembly 16 is connected to a Y-shaped distal end 26a by means of a pair of pins 28. These pins enable the head to flex and conform to the curvature of the skin surface. (Hoffmann, Col. 4 , lines 4-7). Applicants' detachable electrode provides the considerable advantage over the art of allowing the practitioner to "change" the electrode between subjects to prevent any passage of contamination between subjects. In addition, being handheld, the invention pulser can be applied at will to the skin surface and rapidly removed from contact with the skin surface if pain or discomfort is detected.

Accordingly, Applicants respectfully submit that Hofmann fails to disclose each and every element of claim 57 (and by dependent claims, 59-64, 67-68, 72-74, which contain all limitations of claim 57) as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b) and reconsideration and withdrawal of the rejection are respectfully requested.

C. Applicants additionally respectfully traverse the rejection of claims 57-65, 67, 71-73 and 80 as allegedly being anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 3,163,166 to Brant et al. (hereinafter "Brant"). Brant is absolutely silent regarding a handheld pulser having a detachable electrode, as is included in the invention handheld pulser defined by amended claim 57. For example, in Brant's pulser, the electrode is not removed to replace the supply of fluid. Instead, the casing is opened to permit replacement of the fluid cartridge (Brant, Col 6, lines 55-56). Certain of Applicants' dependent claims recite additional features missing from Brant's pulser. For example, Brant fails to disclose an electrically conducting cover for the electrode, as is included in the invention handheld pulser defined by amended claim 59. Instead, in the Brant pulser, the cover 26 is a "slip-on" cap designed to protect the tapered end of the apparatus when the device is not in use (Brant, Col 2, lines 3-6) and electrical contact with skin is made by means of an electrolyte fluid that coats the surface of the freely rotating spherical electrode rather than through an electrically conducting cover for the electrode. In addition, the cover in the Brant pulser is not "absorbent" (as recited in Applicants' claim 61). Thus, Applicants respectfully submit that Brant fails to disclose each and every element of the invention handheld pulser, as defined by present claim 57 (and by dependent claims 58-65, 67, 71-73 and 80, which contain all elements of claim 57) as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection over Brant under 35 U.S.C. 102(b).

The Rejection under 35 U.S.C. § 103

A. Applicants respectfully traverse the rejection of claims 1-4, 6-17, 19-21, 25, 28-30, 32-43, 45-47, 51-54, and 56 under 35 U.S.C. § 103(a) for allegedly being obvious over Weaver (U. S. Patent No. 5,019,034, hereinafter "Weaver") in view of Ariura is respectfully traversed. Applicants' invention method for treating degenerative skin conditions by electroporation-delivered L-ascorbic acid and derivatives thereof, as required by present claim 1, distinguishes over the combined disclosures of Weaver and Ariura by requiring application to a subject (i.e., live) of "at least one electric pulse having sufficient strength and duration to cause electroporation of the skin, thereby delivering an effective amount of the L-ascorbic acid through the stratum corneum of the region of skin so as to improve the skin condition without substantial pain or skin irritation." Applicants' method for electroporation-enhanced dermatological delivery of L-ascorbic acid through the stratum corneum of a subject in need thereof, as defined by claim 28, distinguishes over the combined disclosures of Weaver and Ariura by requiring application to the surface of a region of skin of at least one electric pulse having sufficient strength and duration to topically deliver an effective amount of the L-ascorbic acid or the derivative to the region of skin.

Applicants respectfully disagree with the Examiner's assertion that Weaver teaches a method of "delivering medicaments to the active skin layer with increased efficiency" (Office Action, page 4). The disclosure of Weaver pertains almost exclusively to administration of such relatively stable molecules as glucose or mannitol, but not to labile "medicaments" such as Vitamin C. As is well known in the art, L-ascorbic acid is subject to degradation and rapid loss of activity upon exposure to oxidation, heat, etc. Applicants submit that Weaver's disclosure does not teach or provide reasonable certainty to those of skill in the art that L-ascorbic acid

could be delivered to a subject by electroporation (e.g., without degradation) to improve the condition of skin without substantial pain or skin irritation.

In addition, the skin to which Weaver's compounds are successfully applied using electroporation is excised skin layers removed from cadavers or mice (See Weaver, Examples 1-4). Applicants submit that in Weaver's single *in vivo* study performed on live skin, the results were ambiguous: "Due to sporadic urine output, the result appears positive but some ambiguity remains" (Example 5, Col 14, lines 49-51). Thus, based upon these insufficiencies in the disclosure of Weaver, Applicants respectfully submit that those of skill in the art would lack a reasonable expectation after reading Weaver that L-ascorbic acid could be delivered in a therapeutic dose or that such delivery could be accomplished without substantial pain or irritation to skin of a live subject, such as on the face or hands.

Furthermore, Applicants respectfully submit that Ariura's disclosure pertaining to delivery of Vitamin C by iontophoresis does not overcome the deficiencies of Weaver discussed above. The deficiencies of Ariura for disclosing Applicants' invention methods discussed above apply equally and are incorporated here. In addition, Applicants respectfully submit that Ariura fails to suggest how to modify the method of Weaver to successfully deliver a cosmetic or therapeutic level of L-ascorbic acid, or a derivative thereof, through the stratum corneum of the skin of a live subject while causing no substantial pain or skin irritation because the disclosure of Ariura pertains to iontophoresis and is completely silent regarding electroporation, as Applicants have discussed at length above. Consequently, Applicants respectfully submit that the combined disclosures of Weaver and Ariura fail to suggest Applicants' methods under 35 U.S.C. § 103 for delivery of L-ascorbic acid, or a cosmetically/pharmaceutically acceptable salt, ester or other derivative thereof by electroporation, such as in treatment of degenerative skin disorders. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Applicants respectfully traverse the rejection of claims 1-4, 7-17, 19-21 and 27 under 35 U.S.C. § 103(a) for allegedly being obvious over Sibalis et al. (U. S. Patent No. 5,135,478, hereinafter "Sibalis I") in view of Ariura. Applicants' invention method for treating degenerative skin conditions by electroporation-delivered L-ascorbic acid and derivatives thereof, as required by present claim 1, distinguishes over the combined disclosures of Sibalis I and Ariura by requiring application to a subject (i.e., live) of "at least one electric pulse having sufficient strength and duration to cause electroporation of the region of skin, thereby delivering an effective amount of the L-ascorbic acid through the stratum corneum of the region of skin so as to improve the skin condition without substantial pain or skin irritation." Applicants disagree with the Examiner's assertion in support of the rejection that:

> To have selected Vitamin C as the desired agent to be delivered and then optimized the voltage, frequencies, etc. would have been obvious. It is noted that applicant's recited voltages i.e. 25 V, 100 V etc. are not necessarily electroporation voltages since it is the voltage/current density (i.e. V/cm^2) that determines whether electroporation occurs or not.

(Office Action, page 5).

However, Applicants teach that the field strength in skin depends upon the degree of depth into the tissue and the change in resistivity before and after the breakdown of the stratum corneum: "After breakdown of the stratum corneum, the field strength increased by four orders of magnitude within the epidermis region at a skin depth of 125μm (Figure 3B). Interestingly enough, the increase of field strength always occurred around the edge of the electrodes (Figures 4A and 4B). The area below the center of each electrode had the lowest field" (Specification, page 27, lines 3-7). Thus, Applicants have discovered that voltage is the parameter that determines distribution of the electric field in

the skin for electroporation-mediated delivery of Vitamin C, as is required in the invention methods of amended claims 1 and 28. Further, Applicants have discovered that the combination of pulse strength and duration can be controlled so as to cause electroporation in skin cells, thereby allowing electroporation-mediated delivery of Vitamin C without the subject experiencing substantial pain or skin irritation, as is required in the invention methods of amended claims 1 and 28.

Applicants respectfully submit that the combined disclosures of Sibalis I and Ariura fail to suggest under 35 U.S.C. § 103 that the combination of strength (i.e. voltage) and pulse duration are the parameters to be optimized for cosmetic or therapeutic delivery of Vitamin C to skin of a live subject without substantial pain or discomfort. The disclosure by Sibalis of various current parameters is too general in nature to suggest to those of skill in the art what parameters are appropriate for optimization. In addition, Sibalis and Ariura are silent regarding the size of electrodes or spacing between electrodes to be used for electroporation and hence their combined teachings fail to suggest optimizing these parameters. Thus, Applicants submit that those of skill in the art would require undue experimentation to arrive at Applicants' invention methods in view of the combined disclosures of Sibalis I and Ariura.

Accordingly, Applicants request reconsideration and withdrawal of the rejection.

C and **D.** Applicants also traverse the separate rejections of claims 5, 18, 23-24, 31, 44, 49 and 50 under 35 U.S.C. § 103(a) for allegedly being obvious over Weaver or Ariura in view of the Background of the Invention and of claims 5, 18, and 23-24 over Ariura or Sibalis in view of Ariura and further in view of the Background of the Invention are both respectfully traversed. In each of these rejections, the Examiner acknowledges that Applicants differ in reciting the

L-ascorbic acid provided in a cream, a specific derivative, or at a certain pH which neither Ariura et al. nor Weaver specify (Office Action, page 5, bottom paragraph and page 6, lines 3-4). In addition, to the deficiencies of these references discussed throughout this response with reference to claims 1 and 28, Applicants respectfully submit that the discussion in the Background of the Invention of known compositions used for topical application over prolonged periods of time fails to suggest which parameters and/or combinations of parameters such as cream vs. solution, pH, and chemical derivative, are "result effective." For example, the known formulations commented upon in the Background range in pH value from 7 (i.e., neutral) to 2.2. Applicants respectfully submit that mere "shot-gun" disclosure of parameters in the cited art without indication of which of the many parameters disclosed is to be optimized or what combination of parameters should be used when using electroporation to treat degenerative skin conditions is not sufficient to constitute obviousness under 35 U.S.C. § 103.

E and F. Applicants also respectfully traverse the separate rejection of claims 22 and 48 under 35 U.S.C. § 103(a) for allegedly being obvious over Weaver in view of Ariura and further in view of Chien et al. (U.S. Patent No. 5,042,975) or Sibalis et al. (U.S. Patent No. 5,135,478, hereinafter "Sibalis II") and of claim 22 over Ariura or Sibalis I in view of Ariura, each further in view of Chien or Sibalis II. Applicants disagree with the Examiner's assertion that it would have been obvious to vary the pH of a solution for optimal desired absorption as taught by Chien et al. as well as Sibalis II at Column 17 lines 26-41 or that ascorbic acid in a pH range of 4.0 to 5.0 is obvious as evidenced by Chien et al. and Sibalis II.

In addition to the deficiencies of these references discussed throughout this response with reference to claims 1 and 28, Applicants submit that the disclosure of Sibalis II regarding pH to which the Examiner refers is ambiguous at best, if not contrary to the pH requirements in claims

22 and 48. Sibalis II discloses that "the rate of absorption of a drug is dependent on the pH level; if the system becomes completely acidic, the drug will not be absorbed" (Col 17, lines 28-30). The phrase "completely acidic" is either ambiguous or suggests that any pH below 7 is to be avoided. Thus Applicants submit that the combined disclosures of the cited art fail to suggest Applicants narrow range of 4.0 to 5.0, as required in claims 22 and 48.

G and **H**. Applicants further traverse the separate rejections of claims 25-26 under 35 U.S.C. § 103(a) for allegedly being obvious over Ariura, or alternatively over Sibalis II in view of Ariura, each further in view of one of Lee (U. S. Patent No. 5,250,023, hereinafter "Lee") or Eppstein (U.S. Patent No. 5,445,611; hereinafter "Eppstein") and of claims 26 and 55 over Weaver in view of Ariura are both respectfully traversed. The Examiner bases these rejections on the assertion that use of microabrasion devices as well as chemical enhancers is well known for lowering skin resistance.

Applicants incorporate here the above discussion of the deficiencies of Ariura, Sibalis II and Weaver when taken alone, or taken together, for suggesting the present invention methods. Applicants submit that the disclosures of Eppstein and Lee fail to overcome these deficiencies of the primary references. Eppstein pertains to use of ultrasound and/or chemical enhancers for enhancing transdermal delivery of compounds as compared with passive diffusion, and Lee pertains to use of a "skin needle" as an aid to transdermal delivery from a body patch of a protein or peptide drug dissolved in an ionizing solvent. However, both Eppstein nor Lee are silent regarding methods for electroporation of skin for delivery of Vitamin C to a live subject without substantial pain or skin irritation. Accordingly, Applicants respectfully submit that any combination of the cited art fails to suggest the subject matter of claims 25, 26 and 55 under 35 U.S.C. § 103(a).

I. Applicants respectfully traverse the rejection of claims 57-58, 62-63, 66 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over U. S. Patent No. 5,358,483 to Sibalis (hereinafter Sibalis III) alone or further in view of Sibalis I. Applicants disagree with the Examiner's assertion that Sibalis III "shows a support member in the form of a wrist watch that is capable of being hand held (Office Action, page 8). Applicants' invention "handheld pulser for use as an electroporation apparatus," as required by present claim 57, distinguishes over the disclosure of Sibalis III by requiring a support member that is of a size and shape to be grasped and held by hand and to be applied "by hand" to a skin surface to be treated.

Sibalis III fails to disclose an apparatus suitable for use as a pulse generator that is "hand held." Instead, the support member shown by Sibalis III in Figure 2 is part of a wristwatch and is designed to be strapped around a body part (i.e., by passive attachment). Since Sibalis III is absolutely silent regarding a device that has a support member shaped for grasping by a hand, Applicants submit that Sibalis III fails to disclose each and every element of claim 57 (and claims 58, 62-63, 66 dependent thereon) as would be required to support a rejection for anticipation under 35 U.S.C. § 102(b).

Applicant also respectfully traverses the alternative rejections under 35 U.S.C § 103(a) of claims 57-58, 62-63, 66 over Sibalis III or further in view of Sibalis I for alleged obviousness. Because the Sibalis III device has a support member incorporated within a wristwatch to be strapped about a body part, Applicant submits there is no suggestion provided by Sibalis III to provide a support member having a size and shape suitable for grasping and holding by hand. In addition, Applicants' disagree with the Examiner's assertion that Sibalis III's disclosure of a DC current source (i.e., a battery) could be "considered a pulse generator since the user may turn the

device on and off to generate at least one pulse" (Office Action, page 8). A "pulse generator," as those of skill in the art understand the term, signifies a device that generates automatically a plurality of pulses (e.g., of a selected shape, duration, field strength, and the like). Since the user would have to switch a wrist watch DC source on and off in order to generate a single pulse and Sibalis III is absolutely silent regarding the need or desirability of multiple pulses, Applicants submit that those of skill in the art would not be motivated to modify the disclosure of Sibalis III to arrive at a Applicants' handheld pulse generator, as defined by claim 57.

Moreover, Applicant respectfully submits that the disclosure of Sibalis I does not overcome the above-described deficiencies under 35 U.S.C. § 103 of Sibalis III for rendering obvious Applicants' handheld pulse generator, as defined by claims 57 and 74-75. Like Sibalis III, Sibalis I is absolutely silent regarding a handheld pulse generator having an electrode support that is shaped and sized to be grasped (i.e., held) by hand. In fact, the drawings and disclosure of Sibalis I are devoted almost exclusively to discussion of the electrical circuits used to generate electrical signals suitable for causing transdermal delivery of drugs, such as insulin, into the circulatory system. Hence, Applicants submit that neither Sibalis III nor the combined disclosures of Sibalis III and Sibalis I suggest under 35 U.S.C. § 103(a) Applicants' handheld pulse generator, as defined by amended claim 57 and by claims 58, 62-63 and 66, which depend therefrom and therefore include all limitations of claim 57.

J. Applicants respectfully traverse the rejection of claims 57, 74-75 under 35 U.S.C. § 102(b) for allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Gross (U. S. Patent No. 5,279,544; hereinafter "Gross") alone or alternatively in view of Sibalis I is respectfully traversed. Applicants' invention "handheld pulser for use as an electroporation apparatus," as required by amended claim 57, distinguishes over the disclosure of the cited art by requiring a support member, and a detachable electrode,

wherein said support member is of a size and shape to be handheld, and wherein electrode is operatively connected to a pulse generator.

The device disclosed by Gross is designed for iontophoresis and thus does not include a "pulse generator" as the term is used in Applicants' Specification and claims. In addition, Gross fails to disclose or suggest a "handheld" device suitable for holding by hand while the user moves the device over various parts of the body, such as the hands and/or face of a subject. Instead, Gross discloses a stationary wrist watch-type device that is strapped to one site on the subject for delivery of an active agent over an extended period of time using iontophoresis. Due to these substantial differences between the disclosure of Gross and Applicants' handheld pulse generator, as defined by amended claim 57, Applicants respectfully submit that Gross fails to disclose the invention device under 35 U.S.C. § 102(b) or suggest the invention device, as defined by claims 57, 74-75 under 35 U.S.C. § 103(a).

Moreover, Applicants submit that these deficiencies of Gross are not overcome by combination with the disclosure of Sibalis I, which deficiencies are discussed above apply equally here. In view of the silence of Sibalis I regarding a device having a support designed to be grasped and handheld, Applicants respectfully submit that the combined disclosures of Gross and Sibalis I are insufficient to suggest under 35 U.S.C. § 103(a) Applicants' device as defined by amended claim 57 and by claims 74-75, which depend therefrom and therefore include all limitations of claim 57.

K. Applicants also respectfully traverse the rejection of claim 57 and 76-77 under 35 U.S.C. § 102(b) for allegedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Henley (U. S. Patent No. 5,658,247; hereinafter "Henley") alone or alternatively in view of Sibalis I. Henley fails to disclose a "handheld" pulse generator suitable

for movement over the body during electroporation. The device of Henley's Figure 2 is described as suitable for being "worn as a 'watch band' on an extremity" (Brief Description of the Drawings) and is, hence stationary. Thus, despite Henley's disclosure of vibrational members (piezoelectric crystals), like Sibalis I, Henley's watch band apparatus for iontophoresis is designed to be strapped around a body part and neither discloses or suggests a pulse generator having a support that is shaped and sized for grasping and holding by a hand.

Regarding the combined disclosures of Henley and Sibalis I, Applicants discussion above of the deficiencies of Sibalis I for disclosing or suggesting the device of claim 57 applies equally here. In view of the failure of Sibalis I to disclose or suggest a device that is shaped and sized for grasping and being hand held (and hence being directed to different body parts at the will of the user), Applicants submit that the combined disclosures of Henley and Sibalis I also fail to suggest under 35 U.S.C. § 103(a) the invention handheld pulse generator, as defined by amended claim 57 and by claims 76-77, which depend therefrom and therefore include all limitations of claim 57.

L. Applicants also respectfully traverse the rejection of claim 57 and claims 78 and 79, which dependent therefrom, under 35 U.S.C. § 103(a) as allegedly being obvious over Tuttle (U. S. Patent No. 5,108,363; hereinafter "Tuttle") in view of Sibalis III, alone or further in view of Sibalis I. The above discussion of the deficiencies of Sibalis III and Sibalis I, when taken alone or together, for suggesting the invention handheld pulse generator of claim 57 applies equally here. Applicants respectfully submit that the disclosure of Tuttle regarding a pressure measuring means and a resistance and recorder means, as referred to by the Examiner (Office Action, page 8), is not sufficient to overcome the deficiencies of the Sibalis references for suggesting the invention handheld pulse generator because Tuttle discloses no particular external

structure for the iontophoretic delivery device (the Figures provide only internal wiring schemes). Thus, Applicants respectfully submit that the combined disclosures of Tuttle, Sibalis III and Sibalis I are insufficient to suggest under 35 U.S.C. § 103(a) the invention "handheld" pulse generator, as defined by amended claim 57 and by claims 78 and 79, which depend therefrom and therefore include all limitations of claim 57.

M. Applicants also respectfully traverse the rejection of claims 69-70 for allegedly being obvious under 35 U.S.C. § 103(a) over Hofmann in view of Ariura. Being dependent from claim 57, claims 69 and 70 include all elements of claim 57. Discussion of deficiencies of Hofmann and Ariura for disclosing or suggesting the invention handheld pulse generator, as defined by amended claim 57, either alone or in combination, are set forth above and incorporated here. In addition, as the Examiner acknowledges, Hofmann fails to disclose meander electrodes coated on a flexible sheet. Ariura is unable to overcome these deficiencies of Hofmann because Ariura is also silent regarding any type of handheld device having a support sized and shaped for grasping and holding by hand with a detachable electrode connected to a "pulse generator" (i.e., one that creates a plurality of pulses). Thus, any disclosure by Ariura pertaining to flexible electrodes is insufficient to overcome the above-described deficiencies of the combined disclosures of Hofmann and Ariura for suggesting under 35 U.S.C. § 103(a) the invention handheld pulser of claims 69 and 70.

The Double Patenting Rejection

Applicants respectfully traverse the rejection of claims 1-56 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-54 of U. S. Patent No. 6,302,874. Applicants submit herewith a Terminal Disclaimer disclaiming the terminal part of any patent granted on the subject matter of claims of the above-identified Application No. 09/966,390 that would extend beyond the expiration date of U.S. Patent No. 6,302,874. Any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title to the subject matter of the claims of said patent shall be the same as the legal title to claims of U.S. Patent No. 6,302,874. In view of the Terminal Disclaimer submitted herewith, Applicants submit the rejection is overcome and respectfully request reconsideration and withdrawal of the rejection of claims 1-56 under the judicially created doctrine of obviousness-type double patenting.

Conclusion

In view of the above amendments remarks and the, Applicants submit that all rejections have been overcome. Reconsideration and favorable action on all claims is respectfully requested.

If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: January 10, 2003

June M. Learn, J.D.
Registration No.: 31,238
Telephone: (858) 677-1416
Facsimile: (858) 677-1465

USPTO CUSTOMER NUMBER 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

Enclosure: Exhibit A
Terminal Disclaimer

Applicants: Zhang and Hofmann
Application No.: 09/966,390
Filed: September 27, 2001
Exhibit A: Page 1

EXHIBIT A

Version with Markings to Show Changes Made

In the Claims

Please amend claims 1, 5, 16, 22, 24, 28, 31, 48, 50, 57, 59, 60, 62, 64-66, 69, 71, and 79 as follows:

1. (Amended) A method for treating degenerative skin conditions in a subject in need thereof, said method comprising applying at least one electric pulse to the surface of a region of skin substantially contemporaneously with application thereto of a composition comprising L-ascorbic acid, or a cosmetically/pharmaceutically acceptable salt, ester or [reducing] other derivative thereof, said electric pulse having sufficient strength and duration to deliver an effective amount of the L-ascorbic acid or the derivative thereof through the stratum corneum of the region of skin[, thereby improving] so as to improve the condition of the region of skin without substantial pain or skin irritation.

5. (Amended) The method according to claim 1 wherein the composition is formulated as a cream, spray or lotion.

16. (Amended) The method according to claim [13] 15 wherein the pulse duration is in the range from about 500 μsec to about 50 msec.

22. (Amended) The method according to claim 1 wherein the pH of the composition is in the range from about [4.0] 1.85 to about 5.0 and delivery of the L-ascorbic acid, or the derivative thereof, is enhanced [up to three-fold] as compared with passive delivery thereof.

24. (Amended) The method according to claim 1 wherein the pH of the composition is in the range from about 1.85 to about 3.9 and the and delivery of the L-ascorbic acid, or the derivative thereof, is enhanced [about 30% to about 50%] as compared with passive delivery thereof.

28. (Amended) A method for electroporation-enhanced dermatological delivery of L-ascorbic acid through the stratum corneum of a subject in need thereof, said method comprising applying at least one electric pulse to the surface of a region of skin substantially contemporaneously with application thereto of a composition comprising ascorbic acid, or a cosmetically/pharmaceutically acceptable salt, ester or [reducing] other derivative thereof, said electric pulse having sufficient strength and duration to cause electroporation of the region of skin, thereby topically delivering L-ascorbic acid or a derivative thereof through the stratum corneum of the skin

31. (Amended) The method according to claim 28 wherein the composition is formulated as a cream, spray or lotion.

48. (Amended) The method according to claim 28 wherein the pH of the composition is in the range from about 4.0 to about 5.0 and delivery of the L-ascorbic acid or the derivative thereof is enhanced [up to three-fold] as compared with passive delivery thereof.

50. (Amended) The method according to claim 28 wherein the pH of the composition is in the range from about 1.85 to about 3.9 and the topical delivery of the L-ascorbic acid or the derivative thereof is enhanced [about 30% to about 50%] as compared with passive delivery thereof.

57. (Amended) A handheld pulser for use as an electroporation apparatus, said pulser comprising:

a) a support member of a size and shape to be handheld, and

b) an electrode [having an optional electrically conductive cover] detachably attached to the support member

[wherein said support member is of a size and shape to be handheld, and wherein said electrode is attached to said support member] and [is] operatively connected to a pulse generator.

59. (Amended) A handheld pulser according to claim 57, wherein said electrode [is detachable from said support member] has an electrically conducting cover.

60. (Amended) A handheld pulser according to claim [57] 59, wherein said electrode comprises a porous reservoir for [said] containing and dispensing a therapeutic agent..

62. (Amended) A handheld pulser according to claim 57, further comprising a detachable electrode mounting bracket attached to the support structure for mounting the detachable electrode.

64. (Amended) A handheld pulser according to claim 62, wherein said electrode mounting bracket [is] and electrode have a shape selected from square, round, contoured, [or] and tube shaped.

65. (Amended) A handheld pulser according to claim 64, wherein said tube shaped electrode mounting bracket has a central core comprising an axle, about which said electrode mounting bracket [is] and electrode are rotatable.

66. (Amended) A handheld pulser according to claim [61] 63, wherein said electrode comprises an adhesive layer for attachment of said electrode to said electrode mounting bracket.

69. (Amended) A handheld pulser according to claim 68, said meander type electrode [comprising] comprises an interweaving array of electrically conductive electrode fingers coated on a thin film.

71. (Amended) A handheld pulser according to claim [57] 58, wherein said pulse generator is powered by a battery, optionally contained within said support member.

79. (Amended) A handheld pulser according to claim 57, further comprising a unit to measure and record [the] skin resistance of [the] a subject.